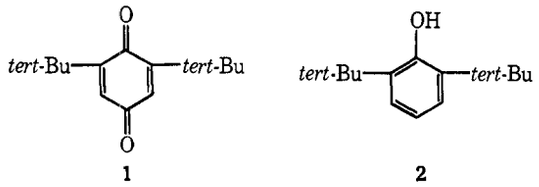
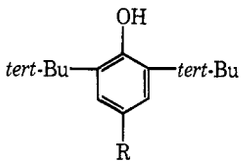
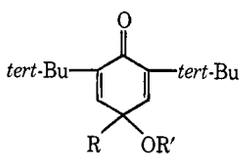


1 2



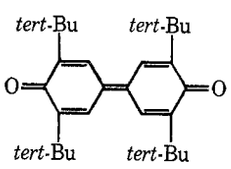
3a, R = alykl
b, R = CH_3
c, R = *tert*-Bu

Therefore, it is surprising that β-manganese dioxide (pyrolusite) oxidizes 2,6-di-*tert*-butyl-4-methylphenol (**3b**) in good yields either to **1** or to 4-alkoxy-2,6-di-*tert*-butyl-4-methyl-2,5-cyclohexadien-1-ones (**4a**), depending on the reaction conditions.



4a, R = CH_3; R′ = alykl
b, R = R′ = CH_3
c, R = CH_3; R′ = CH_3CH_2; $CH_3CH_2CH_2$
d, R = *tert*-Bu; R′ = CH_3

We obtained **1** in 74% yield by treating **3b** with finely divided β-manganese dioxide in a mixture (2/1 w/w) of 40% aqueous sulfuric acid and acetic acid at 60° for 5 hr. Oxidation of **2** under the same conditions gave only a 10% yield of **1**; the main product was 3,3′5,5′-tetra-*tert*-butyldiphenoquinone (**5**). To obtain a good yield of **1** from **3b**, the presence of both water and acetic acid (besides sulfuric acid) is essential. For example, in 40% aqueous sulfuric acid (without acetic acid), only a 15% yield of **1** was obtained after treatment of **3b** with β-manganese dioxide at 60° for 18 hr; in 40% sulfuric acid in acetic acid (water absent), only an 11% yield of **1** was obtained.



5

By oxidation of **3b** with β-manganese dioxide in 40% aqueous sulfuric acid containing methanol (1.5/1 w/w) at 55° for 4 hr, 2,6-di-*tert*-butyl-4-methoxy-4-methyl-2,5-cyclohexadien-1-one (**4b**) was obtained in 60% yield. As by-products, 11% of **1** and 12% of **5** were obtained. Replacement of methanol by ethanol or propanol gave the corresponding ethoxy and propoxy compounds **4c**. When the reaction was carried out in 40% methanolic sulfuric acid (no water present), a 25% yield of **1** was obtained in addition to **5**. No **4b** was detected in this case.

Oxidation of 2,6-di-*tert*-butylphenol (**2**), in which the para position is not blocked by a methyl group, in a 40% aqueous sulfuric acid–methanol mixture at 50° gave no cyclohexadienone. The main product was **5**, and a trace of **1** was found.

The oxidation of 2,4,6-tri-*tert*-butylphenol (**3c**) in a 40% aqueous sulfuric acid–acetic acid mixture gave **1** in 70% yield. In a 40% aqueous sulfuric acid–methanol mixture, a 40% yield of **4d** and a 40% yield of **1** were obtained.

Experimental Section

Oxidation of 2,6-Di-*tert*-butyl-4-methylphenol (3b) to 2,6-Di-*tert*-butyl-*p*-benzoquinone (1).—Twenty grams of **3b** was added to a mixture containing 150 g of 40% aqueous sulfuric acid and 75 g of glacial acetic acid. The mixture was heated to 60° with stirring, and 40 g of finely divided β-MnO_2 (pyrolusite) was added over a period of 2 hr at 60°. After the addition of MnO_2 was completed, stirring was continued for 3 hr at 60°. After the reaction mixture was cooled to room temperature, it was diluted with 600 ml of water and steam distilled. The distillate was extracted with ether, and the ether was allowed to evaporate to give 15 g (75% yield) of **1**.

Oxidation of 2,6-Di-*tert*-butyl-4-methylphenol (3b) to 2,6-Di-*tert*-butyl-4-methoxy-4-methyl-2,5-cyclohexadien-1-one (4b).—Twenty grams of **3b** was added to a mixture containing 150 g of 40% aqueous sulfuric acid and 100 g of methanol. The mixture was heated to 55° with stirring, and 40 g of finely divided β-MnO_2 was added over a period of 2 hr at 55°. After the reaction mixture was cooled to room temperature, it was diluted with 600 ml of water and steam distilled. The distillate was extracted with ether, and the ether was evaporated. Recrystallization of the residue from ethanol gave a 60% yield of **4b**, mp 92–94°.

Registry No.—**1**, 719-22-2; **3b**, 128-37-0; **4b**, 2411-18-9; β-manganese dioxide, 14854-26-3.

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A New Method for the Methylation of Amines

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The introduction of methyl groups into a primary or secondary amine by reductive alkylation with formaldehyde and formic acid derivatives (the Clarke–Eschweiler method[2]) has proved to be a useful method for the preparation of tertiary methylated amines. In some cases, however, complex mixtures have resulted from the multiplicity of side reactions which can occur.[3] Our need for a milder procedure in connection with another problem currently under investigation, coupled with our earlier interest in the chemistry of the cyanoborohydride (BH_3CN^-)[4] ion, led us to examine the feasibility of a formaldehyde–cyanoborohydride system for amine methylation. We describe here a mild and efficient method for the synthesis of tertiary methylated amines of high purity in good yield.

(1) Alfred P. Sloan Foundation Fellow.
(2) M. L. Moore, *Org. React.*, **5**, 301 (1949).
(3) S. H. Pine and B. L. Sanchez, *J. Org. Chem.*, **36**, 829 (1971).
(4) (a) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, **93**, 2897 (1971); (b) R. F. Borch and H. D. Durst, *ibid.*, **91**, 3996 (1969).

TABLE I
REPRESENTATIVE REDUCTIVE METHYLATIONS WITH FORMALDEHYDE–$NaBH_3CN$ IN ACETONITRILE AT 25°

Entry	Compd[a]	Time, hr	Registry no.	Product	Yield, %	Product (deriv) mp, °C[b]
1	Cyclohexylamine	2	34201-87-1	*N,N*-Dimethylcyclohexylamine	84	(178–180)[c]
2	2-Heptylamine	2	34224-22-1	*N,N*-Dimethyl-2-heptylamine	82	(140–142)[d]
3	*endo*-Norbornylamine	2	34287-03-1	*endo*-*N,N*-Dimethylnorbornylamine	75	(218–219)[c]
4	*N*-Isopropylcyclohexylamine	2	34224-23-2	*N*-Methyl-*N*-isopropylcyclohexylamine	87	(123–124)[c]
5	α-Methylbenzylamine	2	3160-90-5	*N,N*-Dimethyl-α-methylbenzylamine	81	(139–140)[c]
6	*N*-Ethylbenzylamine	1	34224-25-4	*N*-Methyl-*N*-ethylbenzylamine	85	(113–114)[c]
7	Aniline	2	2554-80-5	*N,N*-Dimethylaniline	92	(162–163)[c]
8	*p*-Phenetidine	1	34201-88-2	*N,N*-Dimethyl-*p*-phenetidine	85	(138–139)[c]
9	*N*-Propylaniline	2	34201-89-3	*N*-Methyl-*N*-propylaniline	83	(111–112)[c]
10	*m*-Chloroaniline	3	34201-90-6	*N,N*-Dimethyl-*m*-chloroaniline	86	(143–144)[c]
11	*p*-Bromoaniline	1	586-77-6	*N,N*-Dimethyl-*p*-bromoaniline	87	56–57
12	*m*-Nitroaniline	2.5	619-31-8	*N,N*-Dimethyl-*m*-nitroaniline	68	56–58
13	*p*-Nitroaniline	5	100-23-2	*N,N*-Dimethyl-*p*-nitroaniline	46	162–163
				+		
			100-15-2	*N*-Methyl-*p*-nitroaniline	18	148–150

[a] Ratio of amine:formaldehyde:$NaBH_3CN$: entries 1–9, 1:5:1.6; entries 10–12, 1:10:3; entry 13, 1:20:6. [b] All values are in accord with published values where known; satisfactory elemental analyses were obtained for unknown derivatives. [c] Picrate. [d] Hydrochloride.

Reaction of an aliphatic or aromatic amine with aqueous formaldehyde and $NaBH_3CN$ in methanol (our previously reported[4] conditions for reductive amination) afforded a mixture of starting material and partially methylated products. Presumably the formaldehyde is tied up as the hemiacetal in the methanol system, rendering it less reactive in imine formation. A survey of aprotic solvents which were capable of solubilizing $NaBH_3CN$ was undertaken; acetonitrile proved to be the solvent of choice. The results are summarized in Table I.

This procedure is general for a wide variety of aliphatic and aromatic amines. Amines ranging in basicity from pK_a 10.66 (cyclohexylamine) to 2.47 (*m*-nitroaniline) were successfully methylated under these conditions. Even the very weak base *p*-nitroaniline (pK_a 1.00) was converted to a mixture of mono- and dimethylated products (entry 13). Steric hindrance seems to pose no problem; the hindered amine *N*-isopropylcyclohexylamine (entry 4) underwent methylation without difficulty. Because of the mild conditions, the ease of experimental manipulation, and the high yields of pure products, this reaction appears to be the method of choice for reductive methylation of amines.

Experimental Section

Reductive Methylation of "Reactive" Amines ($pK_a > 4$).—The preparation of *N*-methyl-*N*-ethylbenzylamine is typical. To a stirred solution of 675 mg (5 mmol) of *N*-ethylbenzylamine and 2 ml (25 mmol) of 37% aqueous formaldehyde in 15 ml of acetonitrile was added 500 mg (8 mmol) of sodium cyanoborohydride.[5] A vigorous exothermic reaction ensued, and a dark residue separated. The reaction mixture was stirred for 15 min, and then glacial acetic acid was added dropwise until the solution tested neutral on wet pH paper. Stirring was continued for an additional 45 min, glacial acetic acid being added occasionally to maintain the pH near neutrality. The solvent was evaporated at reduced pressure, and 20 ml of 2 *N* KOH was added to the residue. The resulting mixture was extracted with three 20-ml portions of ether. The combined ether extracts were washed with 20 ml of 0.5 *N* KOH and then extracted with three 10-ml portions of 1 *N* HCl. The acid extracts were combined and neutralized with solid KOH and then extracted with three 20-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and evaporated *in vacuo* to give 735 mg (98%) of *N*-methyl-*N*-ethylbenzylamine as a colorless, glpc-pure oil. Reaction with 1.5 g of picric acid in ethanol afforded 1.61 g (85%) of picrate, mp 110–112°. One recrystallization from ethanol gave an analytical sample, mp 113–114°.

Anal. Calcd for $C_{16}H_{18}N_4O_7$: C, 50.79; H, 4.80; N, 14.81. Found: C, 51.00; H, 4.79; N, 14.79.

Reductive Methylation of "Unreactive" Amines ($pK_a < 4$).—The preparation of *N,N*-dimethyl-*m*-nitroaniline is typical. To a stirred solution of 690 mg (5 mmol) of *m*-nitroaniline and 4 ml (50 mmol) of 37% aqueous formaldehyde in 20 ml of acetonitrile was added 950 mg (15 mmol) of sodium cyanoborohydride. Glacial acetic acid (0.5 ml) was added over 10 min, and the reaction was stirred at room temperature for 2 hr. An additional 0.5 ml of glacial acetic acid was added, and stirring was continued for 30 min more. The reaction mixture was poured into 75 ml of ether and then washed with three 20-ml portions of 1 *N* KOH and one 20-ml portion of brine. The ether solution was dried (K_2CO_3) and evaporated *in vacuo* to give 840 mg of crude product as a semisolid. Thin layer chromatographic analysis (alumina, benzene) showed one major spot corresponding to the desired product and a trace of monomethylated material. Crystallization from aqueous ethanol afforded 565 mg (68%) of *N,N*-dimethyl-*m*-nitroaniline as an orange solid, mp 56–58° (lit.[6] mp 60°), homogeneous on tlc.

Acknowledgment.—Acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

(5) Available from Alfa Inorganics, Inc.

(6) "Dictionary of Organic Compounds," Oxford University Press, Cambridge, 1965, p 1190.

Kinetics of Azo Dye Formation. Micellar Effects

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Few references appear in the literature concerning the effects of micelle-forming surfactants on electrophilic

(1) National Science Foundation Undergraduate Research Participant, 1971.